REMARKS

Claims 1-21 are pending in the application. Claims 16-21 have been withdrawn from consideration as directed to non-elected inventions. Claims 1-15 have been rejected.

Claims 1-5, 9-12, and 16-18 have been amended. Claim 15 has been canceled. Rejoinder of Claims 16-21 and reconsideration and allowance of Claims 1-14 and 16-21 in view of the above amendments and following remarks is respectfully requested.

The Rejection of Claim 9 Under 35 U.S.C. § 112, Second Paragraph

Claim 9 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner has indicated that the phrase "high amorphous and nanocrystalline fraction" is unclear. Claim 9 has been amended to recite that the loaded drug is present in the cross-linked polymer in "increased amorphous phase and nanocrystalline fraction" compared to the crystalline state of the original drug. Support for the amendment can be found at page 6, lines 21-26.

In view of the amendment to Claim 9, withdrawal of the rejection is requested.

The Rejection of Claims 10-15 Under 35 U.S.C. § 102(b)

Claims 10-15 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,695,621, issued to Allada. Withdrawal of the rejection is requested for the following reasons.

Claim 10 is an independent claim directed to a method for increasing the drug-loading capacity of a cross-linked polymer that includes treating the cross-linked polymer with a supercritical fluid that does not contain any drugs. Claims 11-15 depend from Claim 10. Claim 10 has been amended. As amended, Claim 10 recites that the polymer treated with the supercritical fluid not containing any drugs is selected from cross-linked cellulose derivatives, starch and its derivatives, and cyclodextrins and their derivatives.

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The Examiner states that the Allada reference describes the treatment of cross-linked polystyrene polymer with supercritical carbon dioxide and concludes that Claims 10-15 are anticipated.

The cited reference provides a method for reducing residual monomers from fat-imbibing copolymer beads by bringing the copolymer beads into contact with a gas in the supercritical state. In the method, supercritical solvent extraction is employed to reduce residual monomers, solvent catalysts, unreacted initiators, and inhibitors. See Col. 4, lines 26-28. Exemplary monomers for making the fat-imbibing polymer beads are described at Col. 3, lines 3-21, of the reference. Alkyl styrenes are the preferred monomers.

In contrast to the cross-linked polymers prepared from synthetic olefinic monomers described in the Allada reference, in the invention as now claimed, the polymer treated with a supercritical fluid is selected from cross-linked cellulose derivatives, starch and its derivatives, and cyclodextrins and their derivatives. Unlike the cross-linked copolymers of the Allada reference, the recited polymers of the claimed invention do not include residual monomers extractable by supercritical fluid.

Because the cited reference fails to exactly describe the invention as now claimed, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

Furthermore, because the cited reference relates to a method for removing residual monomers, solvents, and other impurities from fat-imbibing polymer beads by contacting the beads with a supercritical gas, the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed: a method for increasing the drug-loading capacity of the recited polymers by treatment with a supercritical fluid.

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The Rejection of Claims 1-9 Under 35 U.S.C. § 103(a)

Claims 1-9 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,670,454, issued to Lai et al., in view of WO 99/25322, Carli et al. Withdrawal of the rejection is requested for the following reasons.

As amended, Claim 1 is directed to a process for loading a drug into a cross-linked polymer that includes the steps of (a) pre-treating a cross-linked polymer with substantially pure supercritical fluid, (b) contacting the pre-treated cross-linked polymer with a supercritical fluid containing a dissolved drug, and (c) removing the supercritical fluid, thereby causing the drug to precipitate inside the cross-linked polymer. Claims 2-9 depend from Claim 1.

The cited references fail to teach every element of the claimed invention. The cited references fail to teach or suggest any method for loading a drug into a cross-linked polymer that includes the step of pre-treating the cross-linked polymer with substantially pure supercritical fluid (e.g., that does not include a drug) prior to subsequently contacting the pre-treated cross-linked polymer with supercritical fluid that does include a dissolved drug.

Claim 1 has been amended to clarify the claimed invention. Claim 1 has been amended to recite that the cross-linked polymer is pre-treated with substantially pure supercritical fluid (e.g., that does not contain a drug dissolved therein). Support for the amendment can be found throughout the specification as originally filed. See, for example, page 2, lines 18-21 and lines 25-28, of the published application.

The Lai et al. reference describes a method for crosslinking porous materials made from biodegradable polymers (e.g., collagen, polysaccharides, synthetic polymers, see Col. 3, lines 38-43) by introducing a supercritical fluid containing a cross-linking agent into a chamber containing the polymer to effect crosslinking. The method optionally includes introducing a pure

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supercritical fluid into the chamber subsequent to crosslinking to remove unreacted cross-linking agent from the cross-linked polymer.

The Carli et al. reference describes a method for impregnating a cross-linked polymer with a drug using a supercritical fluid. The Carli et al. reference describes dissolving a drug in a supercritical fluid, contacting the drug containing fluid with a cross-linked polymer to impregnate the polymer with the drug, and then removing the supercritical fluid to provide a drug loaded cross-linked polymer.

Neither the Lai et al. nor Carli et al. references teach the step of contacting a cross-linked polymer with substantially pure supercritical fluid as a pre-treatment for drug loading.

In contrast to the claimed invention, the Lai et al. reference describes delivering a cross-linking agent to a polymer to be cross-linked through the use of a supercritical fluid that includes a dissolved cross-linking agent. The Carli et al. reference describes delivering a drug to a polymer using a supercritical fluid, but fails to describe any pre-treatment of cross-linked polymer to be impregnated by a drug. The cited references fail to teach or even remotely suggest any process that includes pre-treating a cross-linked polymer with a substantially pure supercritical fluid prior to loading that cross-linked polymer with a drug compound.

The claimed invention provides unexpected results. Furthermore, the method of the invention, which includes a pre-treatment step, provides unexpected results with regard to drug loading and the subsequent bioavailability of the loaded drug.

As set forth in the application as originally filed, applicants have surprisingly found that pre-treatment of a cross-linked polymer with pure supercritical fluid provides for a higher degree and more rapid kinetic of the drug loading into cross-linked polymers compared to processes that do not include a pre-treatment step. See page 2, lines 18-21, of the published application. A

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higher thermodynamic activation of the drugs is obtained by the method that includes a pre-treatment step. See page 2, lines 21-22, of the published application.

Referring to Examples 1-3, pre-treated cross-linked polymer provides for increased drug content: 9.1% to 8.2% for nimesulide (Example 1); 16.0% compared to 10.5% for ibuprofen (Example 2); and 7.9% compared to 6.4% for ibuprofen (Example 3). These examples also demonstrate that the crystallinity of the drug is decreased and thus made more bioavailable by the method of the invention that includes pre-treatment of the cross-linked polymer with a substantially pure supercritical fluid: 0% crystallinity compared to 17% crystallinity for nimesulide (Example 1); 0% crystallinity compared to 34% crystallinity for ibuprofen (Example 2); and 24% crystallinity compared to 92% crystallinity for ibuprofen (Example 3).

Not only do the cited references fail to teach or suggest any method that includes pre-treating a cross-linked polymer with a supercritical fluid for any purpose, but the claimed method provides unexpected advantageous results with regard to both increasing the amount of drug that can be loaded into the cross-linked polymer as well as increasing the bioavailability of the loaded drug.

Because the cited references fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious and patentable over the cited references. Withdrawal of the rejection is requested.

Rejoinder of Claims 16-21

Rejoinder of Claims 16-21 is requested. Claims 16-19 relate to a modified cross-linked polymer having enhanced drug-loading properties prepared by treating the cross-linked polymer with a supercritical fluid that does not contain any drug. Claim 20 relates to the modified cross-linked polymer of Claim 16 further including a drug. Claim 21 relates to a pharmaceutical composition containing the drug loaded modified cross-linked polymer of Claim 20. In view of

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the above amendments and foregoing remarks, rejoinder and allowance of Claims 16-21 is respectfully requested.

CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-14 and 16-21 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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